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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/767,431	01/30/2004	Daniel J. Thompson	25871	6428

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EXAMINER	
ARNOLD, ERNST V	
ART UNIT	**PAPER NUMBER**
1616	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/767,431	THOMPSON ET AL.	
	Examiner	Art Unit	
	Ernst V. Arnold	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-27 are pending.

The Examiner has carefully considered Applicant's remarks filed on 2/8/07 but does not find them to be persuasive. This Action is FINAL.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 9 and 24-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Brown et al. (The Journal of Reproductive Medicine 1999, 44(11), 933-938) in view of Stedman's medical dictionary 24th edition 1982, page 334.

Brown et al. disclose the use of a single dose cream formulation of 2% butoconazole nitrate for vulvovaginal candidiasis (Page 933, title, objective, results). Stedman's medical dictionary defines cream as: a semisolid emulsion of either the oil-in-water or the water-in-oil type, ordinarily intended for topical use. Thus, the cream disclosed by Brown et al. is inherently a multiphase formulation. Brown et al. disclose that of the 150 known species of *Candida*, only nine are pathogenic in humans, which are *albicans, glabrata, tropicalis, pseudotropicalis, lusitaniae, crusei, rugosa, parapsilosis* and *guilliermondi* (Page 934, left column). The Examiner interprets this to mean that Brown et al. define candidiasis as being caused by any of these species of *Candida.* Brown et al. disclose that the patients administered the butoconazole cream with an applicator and that the cream was spread over vaginal mucosal surfaces (Page 935, Study

Drugs and their assignment). Brown et al. disclose a cure rate of 92% suing single dose butoconazole cream with a kill rate over 50% in 4 days (Page 936, Table 1 and page 937, Figure 1). Brown et al. disclose that the single application regimen, efficacy and safety support the use of butoconazole for the management of vulvovaginal candidiasis (Page 938, last paragraph).

Response to arguments:

Applicant asserted that Brown et al. do not teach administration of a bioadhesive single dose treatment formulation comprising from about 0.5 to about 5.0% w/w butoconazole nitrate to a vulvovaginal fungal condition caused by a Candida species selected from the group consisting of *dubliniensis, tropicalis, glabrata, parapsilosis, krusei, and lusitaniae* and that Brown et al. only teaches that the single-dose butoconazole is effective in treating *C. albicans* alone. The Examiner still cannot agree. Brown et al. clearly discloses on page 934, lower right column that butoconazole nitrate has a "broad antifungal spectrum, consistently showing high activity against the most important eight non-*albicans* Candida species" and "inhibiting the growth of *C albicans* as well as the non-*albicans* pathogenic species". Furthermore, Brown et al. treated 101 patients with butaconazole nitrate and stated that 10-20% of the cases as non-albicans Candida species, and *C. glabrata* is the second most frequently encountered species (Page 934, left column and page 936, Table 1). Thus, Brown et al. disclose treatment of vulvovaginal fungal condition caused by at least *C. glabrata*. Simply because Brown et al. did not test for the presence of other fungal species of Candida, does not mean that there were not present especially in light of the fact that 10-20% of the cases are caused by non-albicans Candida species. The treatment of other Candida species in the method of Brown et al. is inherent in the method.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Riley (US 5,266,329) in view of Brown et al. (The Journal of Reproductive Medicine 1999, 44(11), 933-938) and Garg et al. (Pharmaceutical Technology Drug Delivery 2001, 14-24) and Droegemueller et al. (Obstet Gynecol. 1984, 64(4), 530-4) and Chen et al. (US 6,267,985).

Applicant claims: A method for the local treatment of a vulvovaginal candidiasis condition diagnosable by a KOH smear test or other fungal speciation test, which comprises: treating said vulvovaginal candidiasis condition caused by a species of Candida selected from the group consisting of dubliniensis, tropicalis, glabrata, parapsilosis, krusei, and lusitaniae by applying to the vaginal tissue of a human a formulation comprising; about 35 to about 45% w/w sorbitol solution; about 3 to about 8% w/w propylene glycol; about 0.001 to about 1% w/w edetate disodium; about 5 to about 11% w/w mineral oil; about 0.5 to about 5% w/w

polyglyceryl -3- oleate; about 0.5 to about 5% w/w glyceryl monoisostearate; about 0.001 to about 1% w/w microcrystalline wax; about 0.5 to about 2% w/w silicon dioxide; about 0.001 to about 1% w/w methylparaben; about 0.001 to about 1% w/w propylparaben; about 25 to about 45% w/w water; and about 0.5 to about 5% w/w butoconazole nitrate; and wherein the treatment is a single dose treatment.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Riley teaches systems and methods of preparation and use that release an antifungal agent such as an imidazole in a controlled manner in a vaginal cavity (Abstract). Riley teaches a composition of (in % wt/wt): 42.895 water; 39.978 sorbitol solution; 2.00 metronidazole; 0.05 EDTA disodium; 4.016 dimethicone; 4.016 mineral oil; 2.713 glyceryl isostearate; 2.713 polyglyceryl-4 oleate; 1.013 colloidal silicon dioxide; 0.452 microcrystalline wax; 0.127 methylparaben; and 0.027 propylparaben (Column 6, lines 18-30). Note the ratio of polyglyceryl-4 oleate to glyceryl isostearate is 1:1. Riley teaches methods of treating a vaginal fungal infection wherein the active antimicrobial agent is an imidazole agent (Claims 4 and 7).

The reference of Brown et al. is discussed in detail above and that discussion is hereby incorporated by reference. Brown et al. teach the use of a single dose cream formulation of 2% butoconazole nitrate for vulvovaginal candidiasis (Page 933, title, objective, results). Brown et al. teach that of the 150 known species of *Candida*, only nine are pathogenic in humans, which are *albicans, glabrata, tropicalis, pseudotropicalis, lusitaniae, crusei, rugosa, parapsilosis* and *guilliermondi* (Page 934, left column). Brown et al. teach that the patients administered the

butoconazole cream with an applicator (Page 935, Study Drugs and their assignment). Brown et al. teach that the butoconazole cream would adhere to the vaginal mucosal surface for a prolonged period and that of the 29% of the patients that reported vaginal leakage only 1% of the patients treated found vaginal leakage unacceptable (Page 935, left column and page 938, left column). Brown et al. teach a cure rate of 92% using single dose butoconazole cream with a kill rate over 50% in 4 days (Page 936, Table 1 and page 937, Figure 1).

Garg et al. teach pharmaceutical excipients for vaginal formulations and list propylene glycol as a humectant; preservative; solvent or cosolvent in the formulations (Page 21).

Droegemueller et al. teach that one dose of 2 % butoconazole nitrate vaginal cream results in a maximum plasma level 24 hours after dosing (Abstract).

Chen et al. teach improved delivery of therapeutic agents, including anti-fungal agents, such as butoconazole, in a composition comprising polyglyceryl 2-4 oleate (Abstract; column 29, line 19 and claim 34, for example).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Riley does not expressly teach a method with about 3 to about 8% w/w propylene glycol in the composition.

Riley does not expressly teach a method with about 0.5 to about 5% w/w butoconazole nitrite in the composition.

Riley does not expressly teach a method comprising teating a vulvovaginal candidiasis condition with a composition comprising polyglyceryl-3-oleate.

Riley does not expressly teach a method wherein the treatment provides peak plasma levels of the butoconazole nitrate at about 6 to about 48 hours after administration and retains activity for at least 4 days.

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to add propylene glycol, as suggested by Garg et al., butoconazole, as suggested by Brown et al. and polyglyceryl-3-oleate, as suggested by Chen et al. to the composition of Riley and produce the instant invention. The instantly claimed limitations of a peak plasma level of administration of butoconazole nitrate at about 6 to about 48 hours after administration is taught by Droegemueller et al. Brown et al. demonstrate the effectiveness for at least 4 days.

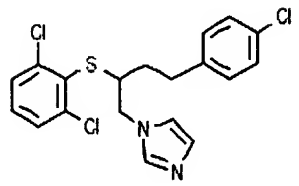
One of ordinary skill in the art would have been motivated to do this because Riley suggests imidazole anti-fungals for use in the composition and Brown et al. demonstrate the effectiveness of butoconazole in single dose. The addition of propylene glycol is known by one of ordinary skill the art as an excipients for vaginal formulations as taught by Garg et al. Chen et al. establish the equivalency of using polyglyceryl-2-oleate, polyglyceryl-3-oleate or polyglyceryl-4-oleate in anti-fungul drug delivery formulations. The adjustment of particular working conditions (e.g., determining the amount of propylene glycol or other ingredients to be used in the formulation and the determination of the type of species of *Candida*) is deemed

merely a matter of judicious selection and routine optimization, which is well within the purview of one of ordinary skill in the art.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to arguments:

Applicant asserts the secondary references provide no motivation to combine their teachings and even if one were to rely on hindsight and combine the cited references the combination would not render obvious each and every limitation of the instant invention as claimed; i.e., methods of treating nonspecified Candida isolates. Applicant asserts that Riley et al. teach utilizing imidazoles upon *C. albicans* and does not teach or suggest the non-albicans as presently claimed. The Examiner cannot agree. First, Riley teaches methods of treating a vaginal fungal infection wherein the active antimicrobial agent is an imidazole agent (Claims 4 and 7) and Brown teaches the range of species affected by butoconazole as discussed above. It is the Examiner's position that it is obvious to one of ordinary skill in the art to use butoconazole nitrate in the method of Riley because Riley directs one of ordinary skill in the art to use imidazole antifungal agents in the method (Claim 7). One of ordinary skill in the art would recognize butoconazole nitrate as an imidazole antifungal agent.



Butoconazole

Secondly, Riley et al. clearly teach delivery systems and methods to treat vaginal fungal infections thus encompassing all fungal microbes that can infect a vagina (claims 1-7). Riley et al. is not limited to a specific microbe. Brown et al. provide the nexus teaching of the range of Candida species treated by butoconazole nitrate. The other secondary references are relied upon to provide teachings on the components in vaginal formulations, which would be known to one of ordinary skill in the art.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

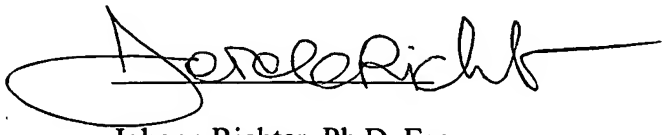
CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ernst V. Arnold whose telephone number is 571-272-8509. The examiner can normally be reached on M-F (6:15 am-3:45 pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ernst Arnold
Patent Examiner
Technology Center 1600
Art Unit 1616



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